Effects of acute serotonin elevation on brain glucose and neurotransmitter metabolism : A 13C MRS study in rats of citalopram administration.

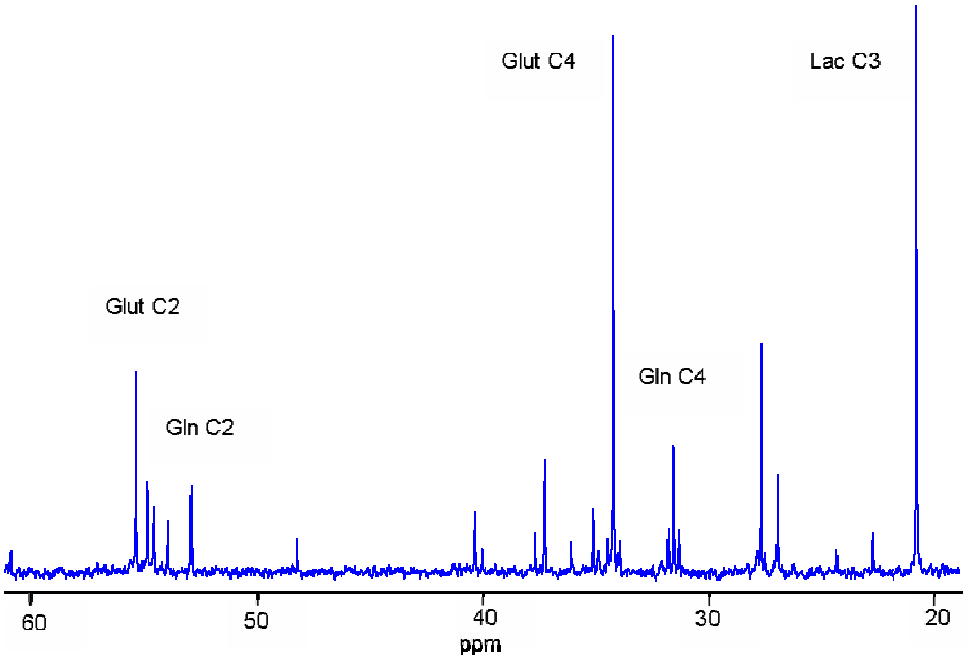
S. R. Williams[1], G. Juszczak[2], C. De-Groote[3], A. H. Swiergiel[2], and B. Deakin[3]

[1]Imaging Science & Biomedical Engineering, The University of Manchester, Manchester, United Kingdom, [2]Department of Animal Behavior, Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Wolka Kosowska, Poland, [3]Neuroscience and Psychiatry Unit, The University of Manchester, Manchester, United Kingdom

Background: Selective serotonin reuptake inhibitors (SSRI) are amongst the most successful drugs used to treat major depression, and imaging studies are starting to play a role in understanding how they act upon the brain. Functional imaging studies in both man[1,2] and animals[3] have demonstrated that SSRI's[1] and serotonin agonists[2,3] induce regional changes in BOLD signal following acute administration. The BOLD signal is thought to reflect local increases in metabolic activity and therefore would be expected to be associated with increased glucose metabolism and increased turnover of the major excitatory neurotransmitter glutamate. Both these parameters can be measured using ^{13}C MRS[4], and here we report the effects of the SSRI citalopram on the metabolism of 1-^{13}C-glucose and 1,2-^{13}C acetate in anaesthetized rats.

Aims: To determine if acute citalopram administration causes increased glucose oxidation and glutamate metabolism in the rat brain.

Methods: Male Sprague-Dawley rats were anaesthetized with α-chloralose injected i.p at 2.5 g/kg. Thirty minutes after anaesthesia rats were injected sc with citalopram at 20 mg/kg (6 rats) or with saline (6 rats), and with 1-^{13}C-glucose (540 mg/kg, i.p.) and 1,2-^{13}C-acetate (500 mg/kg, i.p.). Thirty minutes later rats were decapitated, the brain removed and dissected into 3 parts consisting of frontal cortex and olfactory bulb (forebrain), mid-brain and cerebellum. Brain tissue was frozen and extracted using perchloric acid, freeze dried and samples prepared for ^{1}H MRS and ^{1}H-decoupled, nuclear Overhauser-enhanced ^{13}C MRS in a 9.4T Varian INOVA spectrometer. Samples were dissolved in D_2O with addition of 0.8% ethyleneglycol as a concentration standard. ^{13}C spectra were run overnight and quantified by integration using NUTS software (Acorn NMR, Ca). Intensities were corrected for saturation and nuclear Overhauser effect based on a fully relaxed control acquisition using one sample. ^{1}H spectra were acquired for 2h under non-saturating conditions and processed similarly.



^{13}C spectrum of rat forebrain extract. Resonances form lactate (Lac), glutamate (glut) and glutamine (gln) are shown. The central singlet lines are derived from 1-^{13}C glucose, and the satellite doublets from 1,2-^{13}C actetate

Results A ^{13}C spectrum from a forebrain extract is shown above. The resonance intensities of the C2 and C4 singlets, and the satellite doublets of glutamate and glutamine were quantified and compared using 2-way ANOVA for main effects of brain region and drug treatment, with sub-effect tests for individual brain regions. There were no main effects of brain region. Main effects of treatment (increases in metabolites) were detected for the following: Glutamate C2 in frontal brain; glutamate C4 in mid-brain; glutamine C2 with individual regions not reaching significance; glutamine C4 in frontal and mid-brain. No significant effects of treatment or region were detected for the double-labelled spins, and no effects of treatment were seen in the cerebellum. Analysis of the 1H MRS data showed no significant effects on steady state levels of glutamate or glutamine.

Discussion: The C4 singlets mainly reflect neuronal labelling by glucose, while the doublets indicate labelling by acetate which can only occur in astrocytes. We conclude that citalopram stimulated neuronal glucose oxidation in the cerebrum (increased glutamate C4 and C2 labelling) and also neurotransmitter recycling (increased glutamine C4 and C2). Astrocytic substrate utilization was not stimulated (no increase in double-labelled metabolites). The absence of change in ^{1}H MR spectra indicates that the pool sizes of unlabelled metabolites were unaffected by citalopram. This implies that ^{13}C MRS is a more sensitive method than ^{1}H MRS for detecting changes in neurotransmitter activity.

Refs:

1. McKie et al: **Neuronal effects of acute citalopram detected by pharmacoMRI.** *Psychopharmacology* 2005, **180:**680
2. Anderson et al: **5-HT2C receptor activation by m-chlorophenylpiperazine detected in humans with fMRI.** *Neuroreport* 2002, **13:**1547
3. Stark et al: **Functional magnetic resonance imaging and c-Fos mapping in rats following an anorectic dose of m-chlorophenylpiperazine.** *Neuroimage* 2006, **31:**1228
4. Brenner et al: **Impaired glutamine metabolism in NMDA receptor hypofunction induced by MK801.** *J Neurochem* 2005, **94:**1594